DE NOVO CLASSIFICATION REQUEST FOR EASEVRX

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Virtual reality behavioral therapy device for pain relief. A virtual reality behavioral therapy device for pain relief is a device intended to provide behavioral therapy for patients with pain. Therapy is administered via a virtual reality display which utilizes a software program containing the behavioral therapy content.

NEW REGULATION NUMBER: 21 CFR 890.5800

CLASSIFICATION: Class II

PRODUCT CODE: QRA

BACKGROUND

DEVICE NAME: EaseVRx

SUBMISSION NUMBER: DEN210014

DATE DE NOVO RECEIVED: March 31, 2021

SPONSOR INFORMATION:

AppliedVR, Inc.
16760 Stagg St, Ste 216
Van Nuys, CA 91406

INDICATIONS FOR USE

The EaseVRx System is indicated as follows:

EaseVRx is a prescription-use immersive virtual reality system intended to provide adjunctive treatment based on cognitive behavioral therapy skills and other evidence-based behavioral methods for patients (age 18 and older) with a diagnosis of chronic lower back-pain (defined as moderate to severe pain lasting longer than three months). The device is intended for in-home use for the reduction of pain and pain interference associated with chronic lower back pain.

LIMITATIONS

The sale, distribution, and use of EaseVRx are restricted to prescription use in accordance with 21 CFR 801.109.

Safety and effectiveness have not been demonstrated in patients with moderate to severe depression.

If a user experiences motion sickness, dizziness, headache, or eye strain when using the device, stop use of the device and resume therapy per your doctor's advice.

If you suffer from the following, please consult your doctor before use:

- Hearing and visual impairment
- Hypersensitivity to flashing light or motion
- Injury to eyes, face, or neck that prevents comfortable use of VR
- Have a history of epilepsy, suffer from physical, mental or heart disease
- Have any serious medical condition

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

EaseVRx is an immersive virtual reality (VR) system which delivers 3-D VR treatment that incorporates principles of cognitive behavioral therapy (CBT), other behavioral methods, and mindfulness strategies to treat patients diagnosed with chronic pain. It is a prescription-use device which uses preloaded software content on a proprietary hardware platform to deliver treatment. The EaseVRx device, shown in the figures below, consists of an off-the-shelf VR head-mounted display (Figure 1) with added Breathing Amplifier (Figure 2) and AppliedVR developed software. The Breathing Amplifier is a mechanical attachment added to the commercially available headset which enables diaphragmatic breathing exercises designed to enhance the user's engagement by amplifying the user's exhalation into the on-board microphone. The device is also marketed with an optional hand-held controller to aid in navigating the user interface.

Figure 1: The EaseVRx Headset

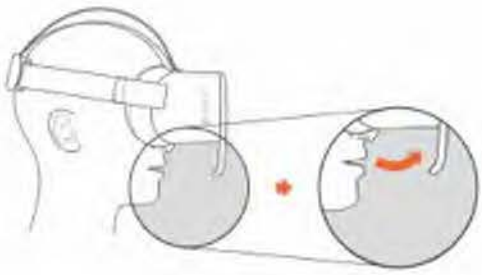

Figure 2: Breathing Apmplifier Component of EaseVRx

EaseVRx is intended for single patient use in the patient's home while the patient is seated. Technical specifications of the EaseVRx head-mounted display are presented in the table below.

Table 1: Technical Specifications

Headset manufacturer and model number	GoerTek Technology Inc. Model: A7510/Pico G2 4K
Rating	5V DC, 2A
Weight	278 (w/o Band), 470 (total)
Frame-rate	72 fps
Screen Resolution	3840 x 2160
Number of pixels horizontally and vertically per eye	Horizontally: 1907 Vertically: 1964
Luminance	Maximum: 0.06nits Minimum: 63.4nits
Interpupillary distance (IPD) and IPD range of the headset	Default 63mm, optical adaptive range is from 55~71mm
Tracking degrees of headset x/y/z 360°	3 degrees of freedom
Field of view per eye	Horizontally: 98 Vertically: 101
Eye relief for prescription lenses	17mm
Range in depths of the virtual content in the software	2m for optics; 3m for launcher software

EaseVRx is designed to follow an 8-week treatment program which delivers a multifaceted combination of pain relief skills training through a sequence of daily sessions ranging from 2-16 minutes in length (average of 6 minutes). Sessions are designed to minimize triggers of emotional distress and motion sickness, as well as to induce relaxation and activation of the parasympathetic nervous system. Similar to multisession behavioral treatments, each week of the treatment program focuses on a specific theme and each daily treatment session is designed to align with this weekly theme in terms of the clinical messaging and content purpose. Initial themes in EaseVRx are focused on developing the skills and understanding of therapeutic principles in VR, including understanding the body, attention and distraction, relaxation strategies, and sleep and pain management, while later themes are focused on the transferring of learning outside of VR, including steps for how to move forward using acceptance and mindfulness while incorporating the behavioral skills learned to daily life. Treatment content is presented chronologically such that informational content (cognitive) is delivered in conjunction with experiential content (behavioral), which allows the user to grow educated in the techniques and skills necessary to mitigate their pain.

Each week provides multiple types of VR experiences, capitalizing on principles of VR design, including immersion, gamification, and interactivity for increased session engagement and improved learning. Different types of experiences, shown in the table below, not only reinforce various pain relief skills but also provide a variety of content that appeals to different user preferences.

Table 2: Categories of Experiences in EaseVRx Treatment

Category	Title		Information or Skills Provided
I	Relaxation/ Interoceptive		Relaxing scenes that change from busy/active to calm reflecting a user's progressively enhanced state of relaxation. These sessions train users to understand and perceive what's going on inside the body as they engage in relaxation.
II	Education		Brief visual and voice-guided lessons about the central nervous system as it relates to pain and breathing. These experiences use anatomical animation to facilitate learning and establish a medical and scientific rationale for the program.
III	Mindful Escapes		Immersive 360° videos with therapeutic narration, guided breathing, music, and visual effects to reinforce mindfulness-based pain relief skills and increase engagement.
IV	Pain Distraction		Interactive games to train pain relief skills related to shifting attentional focus away from pain.
V	Dynamic Breathing		Breathing-based interactive environments to train pain relief skills and induce relaxation. These sessions become increasingly challenging as users increase their skill with diaphragmatic breathing and parasympathetic control.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The face pad, straps, and battery compartment of the headset are considered patient-contacting components of the device, in addition to the optional hand-held controller. The face pad and battery compartment are composed of polyurethane; the straps are composed of silicone, polyurethane polyethylene terephthalate, spandex, and nylon; and the controller is composed of polycarbonate and acrylonitrile butadiene styrene (ABS). All patient-contacting components are categorized as surface contacting with limited contact duration (less than 24 hours cumulative use) of intact skin.

EaseVRx is subject to biocompatibility evaluation in accordance with the International Standard ISO 10993-1: 2009 "Biological Evaluation of Medical Devices Part-1: Evaluation and Testing Within a Risk Management Process." According to the contact

classification and duration of the patient-contacting materials, assessment of the device should include the following tests:

- Cytotoxicity (ISO 10993-5:2009)
- Sensitization Test (ISO 10993-10:2010)
- Intracutaneous Reactivity (ISO 10993-10:2010)

However, considering that these materials have a history of safe use in medical devices, the total cumulative contact duration is low, and that the manufacturing process complies with Quality System Regulations (21 CFR 820.50, 21 CFR 820.80, 21 CFR 820.100, 21 CFR 820.198, and 21 CFR 803), the risk associated with cytotoxicity, irritation, and sensitization are low. Thus, biocompatibility data was not evaluated for EaseVRx.

ELECTROMAGNETIC CAPABILITY & ELECTRICAL SAFETY

EaseVRx was tested according to the following FDA-recognized consensus standards:

- IEC 60601-1:2005 (Modified to be equivalent to (AAMI/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012) "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance." Results demonstrated that the device is compliant to this standard.
- IEC 60601-1-2:2014 "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance-Collateral Standard: Electromagnetic disturbances - Requirements and Tests."
- IEC 60601-1-11:2015 "Medical electrical equipment: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment."

Battery testing

EaseVRx is powered by a 3V rechargeable lithium ion battery, which complies with IEC 60601-1:2005 + A1:2012 and IEC 62133 Edition 2.0 2012-12 "Secondary cells and batteries containing alkaline or other non-acid electrolytes - safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications."

SOFTWARE

The sponsor provided documentation acceptable for software and firmware with a "Minor" Level of Concern (LoC), as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." issued May 11, 2005. The primary risk to patients is delay of treatment due to software/firmware malfunction or failure. Adequate documentation describing the software, firmware, software requirements specification, traceability, revision level history, and cybersecurity provides the foundation that the software will operate in a manner as described in the specifications. A hazard analysis was performed to characterize software risks including device malfunction and measurement related errors.

The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory result.

SUMMARY OF CLINICAL INFORMATION

EaseVRx was evaluated in a single-cohort, double-blinded (participant and analysts), cross-sectional, placebo-controlled, randomized clinical trial. The primary objective of this study was to assess the effectiveness of the EaseVRx therapeutic program in patients with chronic low back pain (cLBP).

The trial consisted of 188 subjects with cLBP randomly assigned to either an EaseVRx treatment group or a sham group. Subjects were first screened for inclusion/exclusion criteria. Once enrolled in the study, subjects participated in a 2-week baseline assessment period where they were required to complete a baseline assessment and one of three pain surveys in order to progress to the treatment phase. The treatment phase consisted of 8-weeks of home use and biweekly surveys. The treatment group received EaseVRx devices and 3-D VR cognitive behavioral based treatment. The sham group received VR devices displaying 2-D non-immersive nature footage with neutral music intended to be distracting and not relaxing or aversive. The sham content was designed not to have any treatment effect. Although each VR device contained software specific to the individual participant's assigned VR treatment group, all device packaging and directions for use were common to both treatment groups. While it was encouraged, participants were not required to select a fixed time to complete each VR session. Participants and study statisticians were blinded to treatment group assignment. In order to get long term data, post-treatment assessments were conducted at 1, 2, 3, and 6 months. Data up to and including the 3-month post assessment were included and reviewed in the De Novo request.

Five primary effectiveness endpoints were defined for this study: average pain intensity and pain interference on activity, mood, sleep, and stress at 8 weekly time points across the 8-week treatment phase. Each endpoint was measured using the Defense and Veterans Pain Rating Scale (DVPRS). A number of secondary endpoints were defined as well, including Patient's Global Impression of Change, various pain coping mechanisms, physical function, sleep disturbance, usability, and treatment satisfaction. Adverse event information was collected to characterize the safety profile of EaseVRx. Patients were encouraged to contact study staff to report any problems encountered during treatment, and a cybersickness was assessed at the end of treatment using a motion sickness and nausea survey.

Results for the pain intensity endpoint demonstrated that 66% of EaseVRx participants and 41% of sham participants achieved >30% reduction in pain intensity. For the EaseVRx group, 46% of participants achieved >50% pain reduction while 26% of the sham participants reached that threshold. In terms of pain interference with activity, 71% of EaseVRx participants and 57% of Sham VR participants achieved >30% reduction, and 56% of the EaseVRx participants achieved >50% reduction. 74% of EaseVRx participants and 60% of the Sham VR participants achieved >30% reduction in pain interference with mood, and 60% of the EaseVRx participants achieved >50% reduction. For pain interference with sleep, 70% of EaseVRx participants and 60% of Sham VR participants achieved >30% reduction, and 60% of the EaseVRx participants achieved >50% reduction. Lastly, 76% of EaseVRx participants and 56% of the Sham VR participants

achieved >30% reduction in pain interference with stress, and 63% of EaseVRx participants achieved >50% reduction.

Results are also shown in the tables below which describe the percent reduction from baseline and the number of patients exhibiting a >30% and >50% change for each primary endpoint. In conclusion, a clinically meaningful (>30%) improvement was observed in the EaseVRx group alone and compared to the sham group.

Table 3: Percent Reduction for Each Primary Endpoint from Pre-treatment to End of Treatment for EaseVRx and Sham Groups

	Pain Intensity	Activity Interference	Sleep Interference	Mood Interference	Stress Interference
EaseVRx	41.6	48.9	51.7	55.7	57.0
Sham VR	23.5	32.1	38.1	36.9	37.4

Table 4: Number (and Proportion) of EaseVRx Participants Showing 30% and 50% Pain Reductions, and the Average Pain Reduction for Each Group

		Pain	Pain Interference			
		Intensity	Activity	Mood	Sleep	Stress
Number (and proportion) of Participants	30% + Reduction	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
	50% + Reduction					
Ave Reduction	30% + Reduction					
	50% + Reduction					

Table 5: Number (and Proportion) of Sham VR Participants Showing 30% and 50% Pain Reductions, and the Average Pain Reduction for Each Group

		Pain	Pain Interference			
		Intensity	Activity	Mood	Sleep	Stress
Number (and proportion) of Participants	30% + Reduction	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)
	50% + Reduction					
Ave Reduction	30% + Reduction					
	50% + Reduction					

The table below shows that a statistically significant difference was observed for all five primary endpoints.

Table 5: Primary Endpoint Overall Efficacy Results
ITT (N=188) and mITT (N=179) Analysis Sets

Analysis Set	ITT (N= 188)		mITT (N= 179)	
Model	condition, time, condition x time		condition, time, condition x time	
Covariates	**Pre Specified** age, gender, race (dichotomized as caucasian and non-caucasian), ethnicity (dichotomized as hispanic and non-hispanic), baseline PROMIS sleep, baseline PROMIS physical function		**Pre Specified** age, gender, race (dichotomized as caucasian and non-caucasian), ethnicity (dichotomized as hispanic and non-hispanic), baseline PROMIS sleep, baseline PROMIS physical function	
Handling of Missing Data	Multiple Imputation		Observed Data	
Statistical Test	**Unadj. p-value**	**Adjusted p-value§**	**Unadj. p-value**	**Adjusted p-value§**
Pain Average	(b)(4)	(b)(4)	(b)(4)	(b)(4)
Pain Interference with Activity				
Pain Interference with Mood				
Pain Interference with Sleep*				
Pain Interference with Stress				

* Condition effect p-value for sleep is shown;
§ Hochberg Step-up corrected p-value.
Source: FDA Submit - Import and Analysis.sas; Analyzed: 2021-08-31

In terms of safety, no participants contacted study staff during the trial to report adverse events of any type. Due to an error with the electronic survey administration, the electronic cybersickness survey was captured at one-month post-treatment instead of at the end of treatment. Additionally, only 147 participants completed the survey. Seven (9.7%) participants from the EaseVRx group and 5 (6.7%) participants from the sham group reported experiencing nausea and motion sickness during the treatment phase of the study. In addition, 15 (20.8%) participants from the EaseVRx group and 4 (5.3%) participants from the sham group reported discomfort with the headset. These adverse events are common and to be expected for VR devices. Furthermore, they were temporary and resolved by discontinuing use or adjusting the device.

Pediatric Extrapolation

EaseVRx is indicated for patients age 18 and older. For medical devices, the FD&C Act defines patients before their 22nd birthday as pediatric patients. In this De Novo request, complete data from patients between 18-81 (mean age 51.4) were used to support the use of the device in adult patients. Because only one patient was evaluated within the age range of 18-22 it was unclear

whether there was enough data to support effectiveness in this population. However, it is appropriate to indicate the device for individuals 18 and older because patients aged 18 to 21 do not carry additional differences or risks relative to the adult patient population studied, and this device has a likely benefit for this group.

LABELING

The labeling (User Manual) meets the requirements of 21 CFR Part 801.109 for prescription devices.

The labeling provides information to users describing the clinical data showing the safety and effectiveness of the EaseVRx device in the intended patient population. It also includes instructions for operating the device and navigating the user interface. Appropriate warnings and precautions are included to avoid hazardous situations and ensure safe use of the device as intended.

The labeling also outlines appropriate cleaning methods for home use.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the virtual reality behavioral therapy device for pain relief and the measures necessary to mitigate these risks.

Identified Risks to Health	**Mitigation Measures**
Adverse tissue reaction	Biocompatibility evaluation
Electric shock or burn or interference with other devices	Electromagnetic compatibility (EMC) testing Electrical, mechanical, and thermal safety testing
Nausea and motion sickness	Clinical performance testing Labeling
Discomfort	Clinical performance testing Labeling
Ineffective treatment	Clinical performance testing Software verification, validation, and hazard analysis Labeling
Use error or improper device use leading to a delay in treatment	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the virtual reality behavioral therapy device for pain relief is subject to the following special controls:

(1) Clinical performance testing under the labeled conditions for use must validate the model of behavioral therapy as implemented by the device and evaluate all adverse events.

(2) The patient-contacting components of the device must be demonstrated to be biocompatible.
(3) Software verification, validation, and hazard analysis must be performed.
(4) Electromagnetic compatibility and electrical, mechanical, and thermal safety testing must be performed.
(5) Labeling must include the following:
    (i) A warning regarding the risk of nausea and motion sickness;
    (ii) A warning regarding the risk of discomfort from the device; and
    (iii) A summary of the clinical testing with the device.

BENEFIT-RISK DETERMINATION

The known probable risks of the device are based on the non-clinical data and the data collected in the clinical study described above. Namely, the study identified adverse events such as nausea, motion sickness, and discomfort due to the headset. The device exhibited an acceptable safety profile in the clinical study, and any adverse events that occurred were temporary and had complete resolution by discontinuing use or adjusting the device. No device-related serious adverse events were observed. The results of the nonclinical testing demonstrated that the device performed as per specifications and the results did not raise concerns regarding risks to the patients.

The probable benefits of the device are also based on data collected in the clinical studies as described above. There is evidence of a clinically meaningful (>30% change) and statistically significant improvement in pain and pain interference DVPRS scores. Results show that 65% of patients in the EaseVRx treatment group achieved a 30% reduction in pain at end of treatment, which was sustained throughout the 1-, 2-, and 3-month follow-up period, whereas only 41% of the sham group achieved a 30% or greater reduction in pain and this improvement was not sustained through follow-up. Additionally, an average of 73% of EaseVRx patients achieved a 30% or greater reduction in pain interference on activity, mood, sleep, and stress, whereas an average of 58% to sham patients achieved a 30% or greater reduction in pain interference on activity, mood, sleep, and stress respectively. Therefore, the clinical study demonstrates a greater improvement in pain and pain interference in the EaseVRx treatment group compared to the sham group.

Sources of uncertainty in the benefits include the effect of concomitant use of prescription and over the counter medications for pain during treatment and imperfect comparator method, specifically that the sham device could have been administering a treatment effect. The use of concomitant medications was addressed by specifying the EaseVRx is intended for adjunctive treatment in the indications for use. Additionally, the clinical data showed a greater improvement in the EaseVRx treatment group compared to the sham group. Even if the sham group did have a treatment effect, the EaseVRx group still demonstrated a greater improvement. This addresses the uncertainty introduced by a potential imperfect comparator method.

PATIENT PERSPECTIVES

The primary and secondary outcome measures in the supportive clinical study were collected using patient reported outcomes. Five patient reported primary effectiveness endpoints were defined: average pain intensity and pain interference on activity, mood, sleep, and stress at 8 weekly time points across the 8-week treatment phase. Each outcome was measured using the Defense and Veterans Pain Rating Scale (DVPRS).

Patient reported secondary outcomes included: Patient Global Impression of Change Scale (PGIC), PROMIS physical function, PROMIS sleep disturbance, Pain Self-Efficacy Questionnaire (PSEQ-2), Pain Catastrophizing Scale (PSCS-4), Chronic Pain Acceptance Questionnaire (CPAQ-8), Patient satisfaction, Positive and Negative Affect Scale (PANAS).

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

> EaseVRx is a prescription-use immersive virtual reality system intended to provide adjunctive treatment based on cognitive behavioral therapy skills and other evidence-based behavioral methods for patients (age 18 and older) with a diagnosis of chronic lower back-pain (defined as moderate to severe pain lasting longer than three months). The device is intended for in-home use for the reduction of pain and pain interference associated with chronic lower back pain.

The probable benefits outweigh the probable risks for EaseVRx. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for EaseVRx is granted and the device is classified as follows:

> Product Code: QRA
> Device Type: Virtual reality behavioral therapy device for pain relief
> Regulation Number: 21 CFR 882.5800
> Class: II